IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Kaufmann, et al.	Art Unit	: 1643
Serial No.	: 09/758,575	Examiner	: Harris, Alana M.
Filed	: January 9, 2001	Conf. No.	: 9437
Title	: GENES DIFFERENTIALLY EXPRESSED IN BREAST CANCER		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION BY DR. ALBERT LAI UNDER 37 C.F.R. § 1.132

I, Albert Lai, a citizen of Canada, residing in United States, hereby declare as follows:

1. I am a Research Investigator II at Novartis (previously Chiron) in Emeryville, California and have been employed at Novartis since 2004 . Prior to my employment with Novartis/Chiron, I was a Scientist I at Sagres, Inc. A copy of my curriculum vitae is attached hereto as Exhibit 1.

2. I understand that the claims in the above-referenced patent application, which are directed to nucleic acid molecules and related compositions and methods, were rejected under 35 U.S.C. § 112, first paragraph, on the grounds that one skilled in the art would not know how to use the claimed invention because the claims are allegedly not enabled. I further understand that this rejection is based, in part, on the assertion that the specification has not provided an enabling disclosure for "implementation of the claimed polynucleotide, which has less than 100% sequence identity with the full length polynucleotide that encodes a variant sequence of SEQ ID NO:2 in assays." For the reasons that follow, I do not agree.

3. Contrary to the assertion of the Patent Office, the specification provides sufficient guidance for a skilled artisan to practice the full scope of the claimed methods without undue experimentation. The specification discloses the amino acid sequence of SEQ ID NO:2. The specification also discloses SEQ ID NO:1, which is a nucleotide sequence that encodes SEQ ID NO:2. The specification describes different types of sequence variations, such as variations that

produce conservative amino acid substitutions (page 12, lines 3-11), truncations or deletions (page 12, lines 28-29), substitutions of charged residues with other charged residues (page 13, lines 22-23), site-directed mutants and mutants produced by alanine-scanning mutagenesis (page 14, lines 1-5). The specification further notes that recombinant DNA methods may be used to produce polypeptides (page 15, lines 9-10). The specification provides an alignment of SEQ ID NO:2 with its *Drosophila* homologue and describes methods for determining the percent identity between two sequences (page 18, line 22 to page 19, line 2). Given this information and knowledge and techniques routine in the art at the time the above-referenced application was filed, it would not require undue experimentation to make and use the claimed compositions and to practice the claimed methods. The specification provides ample guidance for producing and using, for example, a nucleic acid molecule that encodes a polypeptide of SEQ ID NO:2 having five or fewer conservative amino acid substitution, or a nucleic acid molecule that encodes a polypeptide at least 95% identical to SEQ ID NO:2.

4. I further understand that the rejection for lack of enablement is based, in part, on the assertion that "[t]he experimental design presented in the specification continues to lack information regarding the applicability of mutants of polynucleotides and their corresponding encoded products which share limited sequence identity to SEQ ID NO:2 in diagnostic methods relative to breast diseases."

5. This assertion implies that the sole utility of variant sequences is for diagnostic methods and that variant sequences would not be useful for such methods. To the contrary, nucleic acid variants have numerous uses. Such uses are not limited to diagnostic uses. For example, the specification discloses that the claimed nucleic acid molecules can be used to express polypeptides, which in turn can be used as immunogens for the production of antibodies (page 17, line 5, to page 18, line 7; page 19, line 3, to page 21, line 10; and page 24, lines 1-7). Variant nucleic acid molecules can be used to express mutant polypeptides which are tested for biological activity such as receptor binding or proliferative activity (page 14, lines 5-6). The nucleic acid molecules are also useful for production of probes or antisense reagents (page 22, lines 19-25; page 23, lines 1-20). These uses are not exclusive to nucleic acid molecules encoding sequences 100% identical to SEQ ID NO:2. Variant sequences are also applicable such uses. The specification provides sufficient guidance for a skilled artisan to make and use the variant sequences disclosed in the specification.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Printed Name: ALBERT LAI

Signature: 

Date: 12-15-2006

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EXHIBIT 1

CURRICULUM VITAE

Albert CH. Lai, Ph.D.
Birth: June 25, 1974
Citizenship: Canada
510 Lake Blvd., Apt# 100
Davis, CA 95616
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PROFESSIONAL EXPERIENCE

Principle Scientist, Research **July/04 – Present**
Chiron Corporation, Biopharmaceuticals

Primary Responsibilities
- Member of the Oncology Target ID and Validation Team.
- Transition to Chiron the Sagres' Oncogenome™ technology (a method to identify putative oncogenes or tumor suppressor genes using murine retroviral insertion mutagenesis screens).
- Validate mAb (monoclonal antibody) and small molecule gene targets identified in the Oncogenome™ and other genomics and proteomics discovery platforms.
- Manager of two Research Associates/Specialists in the Oncology Antibody Target Validation Team.

Accomplishments
- Successfully validated a mAb oncology target and received Research Management Team approval for pre-clinical development.
- Biology Champion of the WNT therapeutic antibody project team with strategic corporate partner, XOMA Ltd.
- Established several WNT signaling pathway assays for mAb target development.
- Identified additional WNT pathway components for late stage mAb target validation.
- Biology Champion of the Frizzled receptor therapeutic antibody project.

Scientist I, Discovery Research **Oct/02 – June/04**
Sagres Discovery

Primary Responsibilities
- Member of the Target Evaluation Committee. Initiate drug target selection and validation processes from a pool of over 1000 candidate oncogenes.
- Validate mAb (monoclonal antibody) and small molecule gene targets identified in the Oncogenome™.
- Manage the initial high-throughput cDNA Open Reading Frame "ORF" cloning effort for novel full-length human oncogenes.
- Generate and manage the validation process of peptide-based polyclonal antibodies for selected oncology mAb targets.

- Consolidate and interpret in-house quantitative RT-PCR expression profiling, immunohistochemistry data and public microarray data for selected drug targets
- Manager of Research Associates in the Discovery Research Department.

Accomplishments
- Established cell-based assays that measure cell transformation, cell growth, cell death and cell invasion properties using siRNA and vector based-shRNA for target validation.
- Successfully identified and cloned multiple novel human oncogenes drug targets and validated both the oncogenicity and drugability of these targets by cell-based assays.
- Validated multiple polyclonal antibodies for immunohistochemistry applications.
- Identified and validated a novel oncogenic growth factor, DKKL1 (*Patents pending*)
- Established and led the DKKL1 therapeutic antibody program and developed biochemical screens for mAbs generated by in-house mouse hybridoma efforts.

Bioinformatics Scientist, Bioinformatics **Sept/01 – Sept/02**
Sagres Discovery

Primary Responsibilities
- Annotate and curate the first draft of the Oncogenome™.
- Use proprietary (Celera genome browser) and public genomic tools to assemble, annotate, and curate all genes isolated from the Oncogenome™ screen.
- *In silico* determination of mechanistic actions (oncogenes or tumor suppressor) of these genes through examination of patterns of retrovirus integration and consolidation of pathway database information.
- Member of the Drug Target Steering Committee to compile and identify drug targets for internal and external collaborative development

Accomplishments
- Curated and annotated the world largest collection (over 1000) of *in vivo* validated cancer causing genes (The Oncogenome™) by consolidating evidence from proviral insertion tags, public and proprietary genomic databases, and scientific literature.
- Authorship of the original Sagres' patent applications "Novel Compositions and Methods in Cancer" and "Novel Therapeutic Targets in Cancer".

Post-doctoral Scientist **Aug/00 – Sept/01**
Sangamo BioSciences

Primary Responsibility
- Modify Sangamo ZFP™ (Zinc finger protein) technology for validating different oncology targets in cell-based models for pharmaceutical and academic partnerships.
    - Use proprietary ZFP™ technology and *in vivo* promoter analysis technology to re-activate gene expression of the human tumor suppressor CDKN2A/2B locus that is silenced by methylation in lung and bladder cancer.
    - Modify ZFP™ technology by fusion of engineered ZFP with localization and transcriptional repression domains to regulate gene expression of pharmaceutical oncology targets (Chk1 and Chk2).

Accomplishments

- Authorships of two issued patents and a publication in the journal of Proceedings of the National Academy of Sciences of the United States of America (PNAS) in 2004.

Scientific Consultant **Jan/99 – Dec/00**
GeminX Biotechnologies

- The Adenoviral E4ORF4 cell death inducing gene program for cancer therapeutic utilities.

EDUCATION

Bachelors of Science (Honors), Biochemistry **1996**
McGill University, Montreal, Canada

Ph.D. in Biochemistry **2000**
McGill University, Montreal, Canada
Thesis: *The Role of RBP1 in transcriptional regulation by the retinoblastoma family proteins.*
Supervisor: *Dr. Philip E. Branton*

ACADEMIC AND PROFESSIONAL HONORS

McGill University-Faculty of Medicine **July/01**
Dean's Honor Recipient

National Cancer Institute of Canada (NCIC) **Nov/00**
Terry Fox post-doctoral Research Fellowship-Biomedical
Molecular mechanism of de novo methylation induced silencing of the p16 INK4A gene expression.
(Alan P. Wolffe-Sangamo BioSciences)

Canadian Institute of Health Research (CIHR) **Nov/00**
University-Industry post-doctoral fellowship award
Declined.

National Cancer Institute of Canada (NCIC) **June/99**
Terry Fox Research Studentship- Biomedical
The Role of RBP1 in transcriptional regulation by the retinoblastoma family proteins.
(P.E. Branton-McGill University)

ISSUED PATENTS & APPLICATIONS

Lai A., (2003) Discovery of novel splice variants of human DKKL1. **US 60/507,682, WO2005033343.** *(pending)*

Morris DW., Malandro MS., **Lai A.**, Tse C., Fattaey AR. (2004) Novel therapeutic targets in cancer. **US 10/833,833, WO2005104810.** *(pending)*

Morris DW., Malandro MS., **Lai A.**, Tse C., Fattaey AR. (2004) Novel compositions and methods in cancer. **US 10/836,956, WO2005107396.** *(pending)*

Wolffe A., Case CC., Gregory P., **Lai A.**, Snowden A., Tan S., Urnov F. (2002) Modulation of endogenous gene expression in cells. **6,933,113**. *(Issued US Patent).*

Raschke E., **Lai A.**, Urnov F., Wolffe AP. (2002) Modulation of gene expression using localization domains. **6,919,204**. *(Issued US Patent)*

Lai A and Branton PE. (1999) RBP1 polypeptide uses and thereof. **WO0104296**. *(pending)*

BIBLIOGRAPHY

Lai A., Tse, C., Brown DE., Lockhead R. and Fattaey AR. Discovery of novel cancer gene, DKKL1 by genome-wide retroviral mutagenesis. (Manuscript in preparation).

Lai A., Fanidi A., Booher RN. and Fattaey AR.. Identification and characterization of the oncogenic activities associated with two novel splice variants of DKKL1 (Manuscript in preparation).

S. Tan, Guschin D., Davalos A., Lee Y., Snowden AW., Jouvenot Y., Zhang SH., Howes K., McNamara AR., **Lai A.**, Ullman C., Reynolds L., Moore M., Isalan M., Berg L., Campos B., Qi H., Spratt KS., Case CC., Pabo CO., Campisi J. and Gregory PD. ZFP-Targeted Gene Regulation: Genome-Wide Single Gene Specificity. **PNAS**. 2003 Oct 14;**100(21)**:11997-2002.

Lai A., Kennedy BK., Barbie DA., Bertos NR., Yang XJ., Theberge MC., Tsai SC., Seto E., Zhang Y., Kuzmichev A., Lane WS., Reinberg D., Harlow E., Branton PE. RBP1 recruits the mSIN3-histone deacetylase complex to the pocket of retinoblastoma tumor suppressor family proteins found in limited discrete regions of the nucleus at growth arrest. **Mol Cell Biol**. 2001 Apr;**21(8)**:2918-32.

Lai A., Lee JM., Yang WM., DeCaprio JA., Kaelin WG Jr., Seto E., Branton PE. RBP1 recruits both histone deacetylase-dependent and -independent repression activities to retinoblastoma family proteins. **Mol Cell Biol**. 1999 Oct;**19(10)**:6632-41.

Lai A., Marcellus RC., Corbeil HB., Branton PE. RBP1 induces growth arrest by repression of E2F-dependent transcription. **Oncogene**. 1999 Mar 25;**18(12)**:2091-100.

E. Querido., Marcellus RC., **Lai A.**, Charbonneau R., Teodoro JG., Ketner G., Branton PE. Regulation of p53 levels by the E1B 55-kilodalton protein and E4orf6 in adenovirus-infected cells. **J Virol**. 1997 May;**71(5)**:3788-98.

INVITED SEMINARS & MEETING PRESENTATIONS

Lai A., Kennedy BK., Barbie DA., Bertos NR., Yang XJ., Theberge MC., Tsai SC., Seto E., Zhang Y., Kuzmichev A., Lane WS., Reinberg D., Harlow E., and Branton PE. Retinoblastoma tumor suppressor family proteins repress transcription by recruiting the mSIN3 histone deacetylase complex via RBP1. Cancer Genetics & Tumor Suppressor Genes-Cold Spring Harbor. August 16-20, 2000. Cold Spring Harbor, New York, U.S.A. (invited speaker)

Lai A., Kennedy BK., Barbie DA., Bertos NR., Yang XJ., Theberge MC., Tsai SC., Seto E., Zhang Y., Kuzmichev A., Lane WS., Reinberg D., Harlow E., and Branton PE. Retinoblastoma tumor

suppressor family proteins repress transcription by recruiting the mSIN3 histone deacetylase complex via RBP1. The 2000 Molecular Biology of Small DNA Tumor Viruses Meeting. July 9-14, 2000. University of Wisconsin- Madison. U.S.A. (invited speaker)

Lai A., Kennedy BK., Barbie DA., Bertos NR., Yang XJ., Theberge MC., Tsai SC., Seto E., Zhang Y., Kuzmichev A., Lane WS., Reinberg D., Harlow E., and Branton PE. Retinoblastoma tumor suppressor family proteins repress transcription by recruiting the mSIN3 histone deacetylase complex via RBP1. Workshop on Integration of transcription regulation and chromatin structure. April 10-12, 2000. Instituto Juan March de Estudios e Investigaciones. Madrid, Spain. (poster presentation)

Lai A., Lee JM., Yang WM., DeCaprio JA., Kaelin WG. Jr., Seto E. and Branton PE. RBP1 recruits both histone deacetylase- dependent and independent repression activities to RB family proteins. The Imperial Cancer Research Fund 1999 Tumor Virus Meeting on Papovaviruses, Papillomavirus and Adenoviruses. July 13-18, 1999. U. Cambridge, England. (invited speaker)

Lai A., Lee JM., Yang WM., DeCaprio JA., Kaelin WG. Jr., Seto E. and Branton PE. RBP1 recruits both histone deacetylase- dependent and independent repression activities to RB family proteins. Penn State's 18th Summer Symposium in Molecular Biology on Chromatin Structure and DNA Function: 25 years of the Nucleosomes. July 21-24, 1999. Sate College, PA, U.S.A. (poster presentation)

Lai A. and Branton PE. RBP1 represses E2F-activated transcription by a pRB/p130-dependent mechanism that involves specific binding to histone deacetylase. Cancer Genetics & Tumor Suppressor Genes- Cold Spring Harbor. August 19-23, 1998, Cold Spring Harbor, New York, U.S.A. (invited speaker and poster presentation)

Lai A., Marcellus RC., Corbeil HB. And Branton PE. Induction of Growth Arrest by RBP1, a transcriptional repressor associated with p130-E2F complexes. Tumor Suppressor Genes- An AACR Special Conference in Cancer Research Co-sponsored by the National Cancer Institute of Canada. Sept. 26-30, 1997, Victoria Conference Centre, Victoria B.C., Canada (poster presentation)

Lai A., Marcellus RC., Corbeil HB. And Branton PE. Growth Arrest induced by RBP1, a transcriptional repressor associated with p130-E2F complexes. The Imperial Cancer Research Fund 1997 Tumor Virus Meeting on Papovaviruses, Papillomaviruses and Adenoviruses. July 14-19, 1997. U. Cambridge, England. (invited speaker)

Querido E., Teodoro JG., **Lai A.**, Marcellus RC., Ketner G. and Branton PE. Accumulation of p53 induced by adenovirus E1A is prevented by the E4orf6 product which binds directly to p53. Cancer Genetics and Tumor Suppressor Genes, Cold Spring Harbor. Aug. 14-18, 1996. Cold Spring Harbor, New York, U.S.A. (poster presentation)

Querido E., Teodoro JG., **Lai A.**, Marcellus RC., Ketner G. and Branton PE. Adenovirus E1A induced accumulation of p53 which is prevented by the E4orf6 product which binds directly to p53. The 1996 Molecular Biology of Small DNA Tumor Viruses Meeting. July 9-14, 1996. University of Wisconsin-Madison U.S.A. (invited speaker)

REFERENCES:

Available upon request.